

(12) INTERNATIONAL APPLICATION PUBLISHED UNDER THE PATENT COOPERATION TREATY (PCT)

(19) World Intellectual Property Organization International Bureau



(43) International Publication Date  
24 June 2004 (24.06.2004)

PCT

(10) International Publication Number  
WO 2004/053157 A3

(51) International Patent Classification<sup>7</sup>: C12Q 1/68, A01K 67/027, A61K 38/00, 39/00, 48/00

(21) International Application Number: PCT/EP2003/014089

(22) International Filing Date: 11 December 2003 (11.12.2003)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data: 60/432,853 12 December 2002 (12.12.2002) US

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(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, CR, CU, CZ, DE, DK, DM, DZ, EC, EE, EG, ES, FI, GB, GD, GE, GH, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LT, LU, LV, MA, MD, MK, MN, MX, NI, NO, NZ, OM, PG, PH, PL, PT, RO, RU, SC, SE, SG, SK, SY, TJ, TM, TN, TR, TT, UA, US, UZ, VC, VN, YU, ZA, ZW.

(84) Designated States (regional): Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, BG, CH, CY, CZ, DE, DK, EE, ES, FI, FR, GB, GR, HU, IE, IT, LU, MC, NL, PT, RO, SE, SI, SK, TR).

Published:

- with international search report
- before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments

(88) Date of publication of the international search report: 12 August 2004

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

WO 2004/053157 A3

(54) Title: METHODS FOR DIAGNOSING AND TREATING SCHIZOPHRENIA

(57) Abstract: The genes encoding SCYA2, GADD45B, S100A8, CDKN1A, IL1RL1, TGM2, MAFF, SERPINA3, GRO1, CD14, KIAA1075, CHI3L1, SERPINH1, MT1X, KIAA0620, TIMP1, NUMA1, DDIT3 and TOB2, are upregulated in the anterior cingulate of schizophrenic patients compared to normal patients and as such are useful drug targets for schizophrenia. Methods of screening, diagnosing and treating schizophrenia based on these genes are provided. Transgenic nonhuman animals having increased copy number or increased expression levels of these genes are also provided. The transgenic nonhuman animals are used in methods for screening for potential therapeutic agents.

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/14089

A. CLASSIFICATION OF SUBJECT MATTER  
IPC 7 C12Q1/68 A01K67/027 A61K38/00 A61K39/00 A61K48/00

According to International Patent Classification (IPC) or to both national classification and IPC

## B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C12Q

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the International search (name of data base and, where practical, search terms used)

EPO-Internal, MEDLINE, WPI Data, BIOSIS

## C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category <sup>o</sup>	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>VAWTER M P ET AL: "Application of cDNA microarrays to examine gene expression differences in schizophrenia." BRAIN RESEARCH BULLETIN. UNITED STATES 15 JUL 2001, vol. 55, no. 5, 15 July 2001 (2001-07-15), pages 641-650, XP002271622 ISSN: 0361-9230 abstract page 646, column 1, paragraph 3; table 3</p> <p style="text-align: center;">-/-</p>	1-30

Further documents are listed in the continuation of box C.

Patent family members are listed in annex.

### Special categories of cited documents :

- \*A\* document defining the general state of the art which is not considered to be of particular relevance
- \*E\* earlier document but published on or after the International filing date
- \*L\* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- \*O\* document referring to an oral disclosure, use, exhibition or other means
- \*P\* document published prior to the international filing date but later than the priority date claimed

\*T\* later document published after the International filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

\*X\* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

\*Y\* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.

\*&\* document member of the same patent family

Date of the actual completion of the International search

8 March 2004

Date of mailing of the international search report

16. 06. 2004

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# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/14089

**C(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	<p>HAKAK Y ET AL: "Genome-wide expression analysis reveals dysregulation of myelination-related genes in chronic schizophrenia"          PROCEEDINGS OF THE NATIONAL ACADEMY OF SCIENCES OF USA, NATIONAL ACADEMY OF SCIENCE, WASHINGTON, US,          vol. 98, no. 8,          10 April 2001 (2001-04-10), pages 4746-4751, XP002957625          ISSN: 0027-8424          abstract; figure 1; table 1</p> <p>-----</p>	1-30
X	<p>MIRNICS K ET AL: "Analysis of complex brain disorders with gene expression microarrays: schizophrenia as a disease of the synapse"          TRENDS IN NEUROSCIENCE, ELSEVIER, AMSTERDAM, NL,          vol. 24, no. 8,          1 August 2001 (2001-08-01), pages 479-486, XP004273769          ISSN: 0166-2236          the whole document</p> <p>-----</p>	1-30
A	<p>TAMMINGA C A ET AL: "The limbic cortex in schizophrenia: focus on the anterior cingulate."          BRAIN RESEARCH. BRAIN RESEARCH REVIEWS. NETHERLANDS MAR 2000,          vol. 31, no. 2-3, March 2000 (2000-03), pages 364-370, XP002271623          ISSN: 0165-0173          page 364, column 1, paragraph 1 - page 365, column 1, paragraph 2          the whole document</p> <p>-----</p>	1-30
A	<p>BENES F M ET AL: "Increased GABA<sub>A</sub> receptor binding in superficial layers of cingulate cortex in schizophrenics."          THE JOURNAL OF NEUROSCIENCE: THE OFFICIAL JOURNAL OF THE SOCIETY FOR NEUROSCIENCE. UNITED STATES MAR 1992,          vol. 12, no. 3, March 1992 (1992-03), pages 924-929, XP009026657          ISSN: 0270-6474          abstract          page 924, column 1, paragraph 1 - column 2, paragraph 2</p> <p>-----</p> <p style="text-align: center;">-/-</p>	1-30

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/14089

**C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT**

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>DOLAN R J ET AL: "DOPAMINERGIC MODULATION OF IMPAIRED COGNITIVE ACTIVATION IN THE ANTERIOR CINGULATE CORTEX IN SCHIZOPHRENIA" NATURE, MACMILLAN JOURNALS LTD. LONDON, GB, vol. 378, no. 6553, 9 November 1995 (1995-11-09), pages 180-182, XP001122247 ISSN: 0028-0836 the whole document</p> <p>-----</p>	1-30
A	<p>MUNDO E ET AL: "Monocyte chemoattractant protein-1 gene and schizophrenia." AMERICAN JOURNAL OF MEDICAL GENETICS, vol. 114, no. 7, 8 October 2002 (2002-10-08), page 863, XP009026631 Xth World Congress of Psychiatric Genetics; Brussels, Belgium; October 09-13, 2002 ISSN: 0148-7299 (ISSN print) the whole document</p> <p>-----</p>	1-30
A	<p>SCHWARZ M J ET AL: "T-helper-1 and T-helper-2 responses in psychiatric disorders." BRAIN, BEHAVIOR, AND IMMUNITY. UNITED STATES DEC 2001, vol. 15, no. 4, December 2001 (2001-12), pages 340-370, XP002271624 ISSN: 0889-1591 page 345, paragraph 5 – page 350, paragraph 1; table 2</p> <p>-----</p>	1-30
A	<p>TEUSCHER C ET AL: "SEQUENCE POLYMORPHISMS IN THE CHEMOKINES SCYA1 (TCA-3), SCYA2 (MONOCYTE CHEMOATTRACTANT PROTEIN (MCP)-1), AND SCYA12 (MCP-5) ARE CANDIDATES FOR EAE7, A LOCUS CONTROLLING SUSCEPTIBILITY TO MONOPHASIC REMITTING/NONRELAPSING EXPERIMENTAL ALLERGIC ENCEPHALOMYELITIS" JOURNAL OF IMMUNOLOGY, THE WILLIAMS AND WILKINS CO. BALTIMORE, US, vol. 163, 1999, pages 2262-2266, XP002949251 ISSN: 0022-1767 the whole document</p> <p>-----</p> <p style="text-align: center;">-/-</p>	1-30

# INTERNATIONAL SEARCH REPORT

International Application No  
PCT/EP 03/14089

## C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>HARRISON P J: "The neuropathology of schizophrenia. A critical review of the data and their interpretation." BRAIN; A JOURNAL OF NEUROLOGY. ENGLAND APR 1999, vol. 122 ( Pt 4), April 1999 (1999-04), pages 593-624, XP002271625 ISSN: 0006-8950 cited in the application the whole document</p> <p>-----</p>	1-30
A	<p>WO 02/079218 A (WYETH) 10 October 2002 (2002-10-10) paragraph '0106! - paragraph '0108! paragraph '0141! - paragraph '0143! paragraph '0166! - paragraph '0170! paragraph '0174! paragraph '0223! - paragraph '0226! paragraph '0227! - paragraph '0230!</p> <p>-----</p>	1-30
P,A	<p>WO 03/078658 A (NOVARTIS PHARMA GMBH ;NOVARTIS AG (CH); BUXTON FRANCIS PAUL (US);) 25 September 2003 (2003-09-25) the whole document</p> <p>-----</p>	1-30
P,A	<p>EVANS S J ET AL: "DNA microarray analysis of functionally discrete human brain regions reveals divergent transcriptional profiles." NEUROBIOLOGY OF DISEASE. UNITED STATES NOV 2003, vol. 14, no. 2, November 2003 (2003-11), pages 240-250, XP002271626 ISSN: 0969-9961 the whole document</p> <p>-----</p>	1-30

# INTERNATIONAL SEARCH REPORT

International application No.  
PCT/EP 03/14089

## Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1.  Claims Nos.: because they relate to subject matter not required to be searched by this Authority, namely:  
Although claims 9–17, 29 and 30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2.  Claims Nos.: because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3.  Claims Nos.: because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

## Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

see additional sheet

1.  As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2.  As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3.  As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4.  No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:  
1–30 (partially)

### Remark on Protest

The additional search fees were accompanied by the applicant's protest.

No protest accompanied the payment of additional search fees.

**FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210**

Continuation of Box I.1

Although claims 9-17, 29 and 30 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

This International Searching Authority found multiple (groups of) inventions in this international application, as follows:

1. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is small inducible cytokine A2.  
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2. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is growth arrest and DNA-damage-inducible beta.  
---

3. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is S100 calcium binding protein A8.  
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4. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is cyclin-dependent kinase inhibitor 1A p21/Cip1.  
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5. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is interleukin 1 receptor-like 1.  
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6. claims: 1-30 (partially)

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is transglutaminase.

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7. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is V-maf musculo aponeurotic fibrosarcoma oncogene homolog F.

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8. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is serine or cysteine proteinase inhibitor clade A member 3.

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9. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is GRO1 oncogene melanoma growth stimulating activity alpha.

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10. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is CD14 antigen.

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11. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is tensin 2.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

12. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is chitinase 3-like 1, cartilage glycoprotein-39.

---

13. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is serine or cysteine proteinase inhibitor clade H.

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14. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is metallothionein 1X.

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15. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is KIAA0620 protein.

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16. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is tissue inhibitor of metalloproteinase 1.

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17. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is nuclear mitotic apparatus protein 1.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

18. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is DNA-damage-inducible transcript 3.

19. claims: 1-30 (partially)

Method for screening or diagnosing for schizophrenia wherein the expression of a gene is determined, methods of treatment, non-human transgenic animals, and methods of screening based on the presence/production of said gene, wherein said gene is transducer of ERBB2.

**INTERNATIONAL SEARCH REPORT**

International Application No  
PCT/EP 03/14089

Patent document cited in search report		Publication date		Patent family member(s)	Publication date
WO 02079218	A	10-10-2002	WO	02079218 A1	10-10-2002
WO 03078658	A	25-09-2003	WO	03078658 A2	25-09-2003